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Peri-procedural Risk with Urgent Carotid Artery Stenting: A Population based Swedvasc Study

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WHAT THIS PAPER ADDS

This is the first nationwide study that investigates the relationship between the timing of intervention (CAS) after onset of neurologic events, and peri-operative complications. Our data support previous data that CAS within 1 week does not confer an increased risk. Therefore, in patients who are neurologically stable and have an indication for intervention, CAS should not be delayed.

Objectives: Current European Society for Vascular Surgery guidelines recommend that patients with a symptomatic carotid stenosis should be operated on within 14 days of onset of symptoms. Recent reports indicate that carotid endarterectomy (CEA) within 2 days of a neurological event may be associated with a higher peri-procedural risk of stroke. Whether urgent carotid artery stenting (CAS) carries a similar high risk is unclear. The aim of this study was to analyze if urgent CAS increases the peri-procedural risks.

Methods: Retrospective analysis of all CAS registered in Swedvasc, a validated nationwide registry, between January 1, 2005, and March 20, 2014. Only symptomatic patients treated for a stenosis of the internal carotid artery were included. Patients were categorized according to time from index event to surgery; 0–2 days, 3–7 days, 8–14 days, and 15–180 days. Primary outcome was 30 day combined stroke and death rate.

Results: 323 patients underwent CAS for symptomatic carotid artery stenosis. The demographic and clinical data were similar in the groups. No procedure related complications or deaths were observed in the urgent CAS group. The 30 day combined stroke and death rate did not differ significantly between the groups; zero of 13 (0%; 95% CI 0–26.6) in the group treated 0–2 days versus four of 85 (4.7%; 95% CI 1.5–11.9), at 3–7 days, five of 80 (6.3%; 95% CI 2.4–14.1) at 8–14 days, and six of 145 (4.1%; 95% CI 1.7–8.9) for the patients treated at 15–180 days ($p = .757$). Stroke and death were not more frequent for patients treated within 1 week compared with after 1 week: 4 out of 98 (4.1%; 95% CI 1.3–9.0) versus 11/225 (4.9%; 95% CI 2.7–8.6) ($p = .751$).

Conclusions: In this national registry study, CAS performed within 1 week of the onset of a neurologic event was not associated with an additional risk of a peri-operative complication compared with those treated subsequently.

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INTRODUCTION

The risk of recurrent stroke after a transient ischemic attack (TIA) or a minor stroke is very high early after the first incident, up to 10% the first week.[1–4] The majority of all strokes that occur within 30 days of a TIA occur within the first 48 hours of the index event.[5–8] Data from ECST and NASCET showed that for patients with a symptomatic carotid stenosis, carotid endarterectomy (CEA) is most beneficial when performed within the first 2 weeks,[9,10] and current guidelines recommend revascularization within the first 2 weeks of the qualifying event.[11–13]

Although the literature is disparate, some recent reports have questioned the benefit of very early CEA due to a potential risk of increased peri-operative complications.[14–18] Whether urgent carotid artery stenting (CAS) carries a high risk is unclear.

There is evidence from randomized trials of an increased risk with CAS compared with CEA.[19–21] Thus, CAS could be even more questionable in the acute period since an unstable plaque increases the risk of embolization during

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passage of the wire, protection device, or stent across the lesion. Magnetic resonance imaging data from the ICSS study showed a three times higher incidence of new ischemic lesions after CAS than CEA.[22] Soft, lipid rich plaque, pre-occlusive lesion, and plaque ulceration increase the peri-procedural stroke risk for CAS.[23,24] However, the possible increased risk of intervention must be counterbalanced against the risk of recurrent stroke in this acute phase. Studies that report risks with urgent CAS are few and include a limited number of patients.[25–30]

The aim of this retrospective nationwide cohort study was to determine the procedural risk of CAS for symptomatic carotid stenosis in relation to the time from the qualifying neurological event.

MATERIALS AND METHODS

Study design

A retrospective nationwide cohort study of all patients in the National Swedish Registry of Vascular Surgery (Swedvasc) treated by CAS between January 1, 2005, and March 20, 2014. The regional ethics committee in Stockholm approved the study (No 2013/2191).

Swedvasc data

The Swedvasc registry has had national coverage since 1994 (version 1.0), and includes *all* centers performing CEA and/or CAS in the country. Procedure data are recorded along with basic demographics and risk factors. The follow up protocol includes clinical examination and registration of peri-operative complications at 30 days. Mortality data are retrieved directly from the Swedish National Population Registry and are updated monthly. Causes of death are not included in the Registry. Before May 2008 the parameter "heart risk" included atrial fibrillation in Swedvasc but not thereafter.

Cases with incomplete Swedvasc data for date of qualifying event or outcome data have been completed by retrieving charts from the hospital that carried out the operation and/or was responsible for the follow up to reach 100% follow up.

The external validity of Swedvasc is high. For example, the external validity for carotid surgery is 93.6% compared with the Swedish Hospital Discharge Register (SHDR), and mortality data from the population registry are 100% accurate.[31] Data on reason for not performing CEA, use of statins and antiplatelet drugs post-operatively, degree of ipsilateral and contralateral stenosis, and protection devices used were retrieved from patient charts.

The study period covered 9 years (2005–2014). To explore whether the strategies for treating symptomatic carotid stenosis had changed during that time, the period was divided into two parts: January 2005 to August 2009, and August 2009 to March 2014.

Study population

Only procedures for internal carotid artery stenosis were included in this report. Interventions solely to the common carotid were excluded, as were indications other than ICA stenoses (dissections, aneurysms, and trauma). Only bare metal stenting was included in the analyses, and covered stent grafts and percutaneous transluminal angioplasty (PTA) alone were excluded. CAS cases performed with synchronous intracranial or aortic arch interventions were also excluded. Patients operated on bilaterally were identified, and if they were more than 30 days apart both operations were recorded separately and included in the analysis.

Definitions

A symptomatic stenosis was defined as all ipsilateral carotid artery events within 180 days prior to the intervention. Non-hemispheric symptoms and ipsilateral carotid artery events >180 days were excluded. The qualifying event is the neurological event for which the patient received medical advice in the healthcare system. The qualifying events were categorized into TIA, amaurosis fugax, crescendo TIA, minor and major stroke. The Registry (for the time period studied) only includes data on minor or major stroke, so a valid reclassification into the Rankin scale is not possible. Time to intervention was defined as the number of days from the qualifying event to the day of intervention (0–180 days).

Definitions included: renal insufficiency with creatinine >150 μmol/L; hypertension on medication or a diastolic blood pressure of ≥110 mmHg; diabetes treated with insulin, oral medication or diet; and smoking by current smoker (including quit within the last 4 weeks) or non-smoker which includes ex-smoker and people who have never smoked.

Peri-operative complications included any stroke (ipsilateral, contralateral and vertebrobasilar stroke, including intracerebral bleeding), acute myocardial infarction (AMI), and death within 30 days of the procedure. Stroke included any new or worsened focal neurologic deficit (both minor and major stroke) lasting for more than 24 hours. An AMI was defined as a rise and/or fall of cardiac biomarker values (troponin I) with at least one value above the reference limit and with at least one of the following: symptoms of ischemia: new or presumed new, significant ST segment T-wave changes or new left bundle branch block; development of pathological Q waves in the ECG; imaging evidence of new loss of viable myocardium; identification of an intracoronary thrombus by angiography or autopsy.

Statistical analyses

According to a previous Swedvasc study on CEA patients[14] all patients were categorized into different groups depending on the interval between qualifying event and intervention: 0–2 days, 3–7 days, 8–14 days, and 15–180 days. For comparison with other publications[25,26,32] of urgent treatment for carotid artery stenosis, a secondary analysis was also performed with an alternative categorization: 0–7 days, 8–14 days, 15–28 days, and 29–180 days. Because of limited power we also compared 0–7 days versus 8–180. The primary outcome was the 30 day combined stroke and death rate. The secondary outcome was the 30 day combined stroke, AMI, and death rate.

Continuous data are presented with mean and standard deviation (SD) and median and interquartile range (IQR) whenever applicable. The Fisher exact test was used for categorical data whenever possible (if not, chi-square) and a *t* test was used for continuous data; all tests were two sided and statistical significance was defined as $p < .05$. Confidence intervals for proportions were calculated with the modified Wald method (Graphpad.com). All other data were analyzed using IBM SPSS statistics version 22.

RESULTS

Patient characteristics

In total, 323 patients (average age 71 years, 70% men) underwent CAS for symptomatic carotid stenosis between January 1, 2005, and March 20, 2014: 138 with TIA (42.7%), 118 minor stroke (36.5%), 61 amaurosis fugax (18.9%), five major stroke (1.5%), and one crescendo TIA (0.3%) (Table 1). Intervention was performed a median 13 days after the

Table 1. Baseline characteristics in relation to time to CAS for 323 patients.

	Time to CAS, days				
	0–2	3–7	8–14	15–180	*p*
Patients, *n*	13	85	80	145	
Male sex, *n* (%)	10 (76.9)	58 (68.2)	60 (74.1)	98 (67.6)	0.620
Age, yrs (SD)	69 (6.4)	71 (8.7)	72 (9.3)	70 (8.7)	0.306[a]
Octogenarians, *n* (%)	2 (15.4)	14 (16.5)	17 (21.3)	24 (16.6)	0.811
Current smokers ($N = 257$), *n* (%)	2 (16.7)	19 (30.6)	19 (31.1)	27 (22.0)	0.350
Comorbidities, *n* (%)					
Cardiac disease ($N = 265$)	4 (30.8)	32 (37.6)	29 (35.8)	64 (44.1)	0.321
Pulmonary disease ($N = 259$)	3 (23.1)	9 (10.6)	11 (13.6)	15 (10.3)	0.597
Diabetes mellitus ($N = 304$)	5 (38.5)	21 (24.7)	21 (25.9)	35 (24,1)	0.880
Hypertension ($N = 303$)	10 (76.9)	62 (73.8)	61 (75.3)	108 (75,0)	0.939
Renal insufficiency ($N = 314$)	2 (16.7)	5 (6.0)	5 (6.4)	7 (5.0)	0.445
Neurologic event, *n* (%)					
Amaurosis fugax	2 (15.4)	15 (17.6)	9 (11.1)	35 (24.1)	0.119
TIA	2 (15.4)	37 (43.5)	37 (46.3)	62 (42.8)	0.221
Minor stroke	8 (61.5)	30 (35.3)	32 (39.5)	48 (33.1)	0.194
Crescendo TIA	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0.384
Major stroke	1 (7.7)	3 (3.5)	2 (2.5)	0 (0.0)	0.052
Ipsilateral stenosis[b]					0.110
<50%	1 (7.7)	4 (4.7)	4 (4.7)	4 (2.8)	
50–69%	2 (15.4)	25 (29.4)	27 (33.8)	46 (31.7)	
≥70%	9 (69.2)	56 (65.9)	49 (61.3)	94 (64.8)	
Contralateral stenosis ($N = 316$)[b]					0.961
<50%	9 (75.0)	57 (67.9)	55 (68.8)	92 (65.7)	
50–69%	0 (0.0)	12 (14.3)	9 (11.3)	20 (14.3)	
≥70%	1 (8.3)	8 (9.5)	8 (10.0)	13 (9.3)	
Occlusion	2 (16.7)	7 (8.3)	8 (10.0)	15 (10.7)	
Indication for endovascular approach					0.154
RCT	1 (7.7)	10 (11.8)	10 (12.5)	18 (12.4)	
Restenosis	0 (0.0)	2 (2.4)	3 (3.8)	18 (12.4)	
Previous neck radiation or neck surgery	1 (7.7)	9 (10.6)	13 (16.3)	22 (15.2)	
Comorbidity	2 (15.4)	28 (32.9)	22 (27.5)	36 (24.8)	
Surgical inaccessible stenosis	3 (23.1)	13 (15.3)	14 (17.5)	16 (11.0)	
Patients choice	0 (0.0)	3 (3.5)	3 (3.8)	9 (6.2)	
Not specified reason	6 (46.2)	20 (23.5)	15 (18.8)	25 (17.2)	
Protection device ($N = 322$), *n* (%)					0.047
None	2 (15.4)	9 (10.6)	9 (11.3)	10 (6.9)	
Occlusion balloon	0 (0.0)	5 (5.9)	6 (7.5)	7 (4.8)	
Filter	9 (69.2)	38 (44.7)	37 (46.3)	99 (68.3)	
Reversed Flow	2 (15.4)	32 (37.6)	26 (32.5)	26 (17.9)	
Postop medication					
Statins ($N = 303$), *n* (%)	11 (84.6)	72 (84.7)	64 (80.0)	122 (84.1)	0.885
Antiplatelet therapy ($N = 311$)					0.603
Single antiplatelet *n* (%)	2 (15.0)	5 (5.9)	3 (3.8)	15 (10.3)	
Dual antiplatelet *n* (%)	10 (76.9)	71 (83.5)	67 (83.8)	108 (74.5)	
Anticoagulation, *n* (%)	1 (7.7)	7 (8.2)	4 (5.0)	6 (4.1)	

CAS = carotid artery stenting; TIA = transient ischemic attack.

[a] *p*-Values were calculated by chi-square and *t* tests.

[b] Degree of stenosis according to the NASCET criteria.

qualifying event (IQR 7—29). The reasons for choosing an endovascular approach rather than CEA are specified in Table 1. Protection devices were used in 90.6% of the patients. Several different protection devices were used as listed in Table 1: a filter was most frequently used (58%), followed by reversed flow (Neuro Protection System, WL Gore, Flagstaff, AZ, USA).

Post-operatively, 82.3% were prescribed dual antiplatelet therapy for at least 1 month, 9.6% anticoagulation therapy, and 89.0% were prescribed statins.

The numbers of patients in the respective time groups were 13 patients 0—2 days; 85 patients 3—7 days; 80 patients 8—14 days; and 145 patients 15—180 days. For the secondary analyses the respective numbers were 98 patients 0—7 days; 80 patients 8—14 days; 62 patients 15—28 days, and 83 patients 29—180 days.

There were no statistically significant differences between the groups with respect to background data, comorbidities, and ipsi- or contralateral grade of stenosis (Table 1). Major stroke as the reason for attending a health care center was slightly more common in the group treated within 2 days than the other groups (7.7% vs. 3.5%, 2.5% and 0.0% respectively, $p = .052$).

For the secondary analyses there were no significant differences between the different time groups with respect to comorbidities and background data.

Procedure related adverse events

Major peri-operative complications (stroke/death/AMI) occurred in 21 of the 323 patients (6.5%). The thirty day stroke and death rate for the whole group was 4.6%, and the stroke rate was 4.0%. Four (1.2%) died within 30 days from the procedure and seven (2.2%) had a myocardial infarction.

Rates of peri-operative complications based on time from onset of symptoms to intervention are shown in Table 2. In the group treated within 2 days of the qualifying event, no patients (0 of 13 patients) suffered from procedure related stroke or death. However, the 30 day combined stroke and death rate did not differ significantly between the groups: zero of 13 (0%; 95% CI 0—26.6) in the group treated 0—2 days versus four of 85 (4.7%; 95% CI 1.5—11.9) at 3—7 days, five of80 (6.3%; 95% CI 2.4—14.1) at 8—14 days, and six of 145 (4.1%; 95% CI 1.7—8.9) for the patients treated at 15—180 days ($p = .757$).

Stroke and death were not more frequent for patients treated within 1 week of the onset of the qualifying event than after 1 week: four of 98 (4.1%; 95% CI 1.3—9.0) versus 11 of 225 (4.9%; 95% CI 2.7—8.6) ($p = .751$).

The secondary endpoint, 30 day combined stroke, death, and AMI, was also none (0 of 13) in the group treated within 2 days versus seven of 85 (8.2%; 3.8—16.3), six of 80 (7.5%; 3.2—15.7), and eight of 145 (5.5%; 2.7—10.7) for the patients treated at 3—7 days, 8—14 days, and 15—180 days respectively ($p = .640$).

In the secondary analysis, with four different time periods the combined stroke and death rate were similar for all subgroups: 4.1% (1.3—9.0) for the group treated in 0—7 days versus 6.3% (2.4—14.2) treated in 8—14 days, 4.8% (1.1—13.8) in 15—28 days, and 3.6% (0.1—10.5) in 29—180 days (Table 3).

Time trends

In the first half of the study period (January 2005 to August 2009), 4.9% of the symptomatic carotid stenoses in Sweden were treated by CAS ($n = 187$), and the median interval from the qualifying event to intervention was 15 days. The 30 day stroke and death rate during this period was 4.9%. In the second time period (August 2009 to March 2014), the rate of patients treated by CAS had decreased to 3.4% ($n = 136$). The median time to intervention had decreased from 15 to 10 days. The 30 day stroke and death rate during this study period was 5.9%. In the first half of the study period, nine centers performed CAS, seven of them continued in the second time period.

DISCUSSION

In this nationwide study, no significant differences between patients that underwent CAS within 2 days or within 1 week compared with those with delayed intervention were observed. In addition, there was no trend towards an increased risk with an early CAS procedure either with the primary (stroke/death) or secondary endpoint (stroke/death/AMI). On the contrary, no peri-procedural complication or death was observed among those treated within the first 2 days of the onset of symptoms.

There are limited previous data regarding CAS in the early phase after a neurological event. The CAPTURE registry, a retrospective cohort study with a total of 482 symptomatic

Table 2. Procedural adverse events.

	Time to CAS (days)				
	0—2 ($n = 13$)	3—7 ($n = 85$)	8—14 ($n = 80$)	15—180 ($n = 145$)	p
Stroke, n (%)	0 (0.0)	3 (3.5)	5 (6.3)	5 (3.5)	0.626
AMI, n (%)	0 (0.0)	3 (3.5)	2 (2.5)	2 (1.4)	0.602
Deaths, n (%)	0 (0.0)	0 (0.0)	3 (3.8)	1 (0.7)	0.126
Stroke/death, n (%)	0 (0.0)	4 (4.7)	5 (6.3)	6 (4.1)	0.757
(95% CI)	(0—26.6)	(1.5—11.9)	(2.4—14.1)	(1.7—8.9)	
Stroke/death/AMI, n (%) (95%CI)	0 (0.0)	7 (8.2)	6 (7.5)	8 (5.5)	0.640
	(0—26.6)	(3.8—16.3)	(3.2—15.7)	(2.7—10.7)	

AMI = acute myocardial infarction; CAS = carotid artery stenting; CI = confidence interval.
p-Values were calculated by the chi-square test.

Table 3. Procedural adverse events (secondary time classification).

	Time to CAS (days)				
	0–7 ($n = 98$)	8–14 ($n = 80$)	15–28 ($n = 62$)	29–180 ($n = 83$)	p
Stroke, n (%)	3 (3.1)	5 (6.3)	2 (3.2)	3 (3.6)	0.706
AMI, n (%)	3 (3.1)	2 (2.5)	1 (1.6)	1 (1.2)	0.688
Deaths, n (%)	0 (0.0)	3 (3.8)	1 (1.6)	0 (0.0)	0.091
Stroke/death, n (%)	4 (4.1)	5 (6.3)	3 (4.8)	3 (3.6)	0.864
(95%CI)	(1.3–9.0)	(2.4–14.2)	(1.1–13.8)	(0.1–10.5)	
Stroke/Death/AMI, n (%)	7 (7.1)	6 (7.5)	4 (6.5)	4 (4.8)	0.900
(95% CI)	(3.3–14.3)	(3.2–15.7)	(2.1–15.9)	(1.5–12.1)	

AMI = acute myocardial infarction; CAS = carotid artery stenting; CI = confidence interval.
p-Values were calculated by the chi-square test.

patients treated with CAS found an increased stroke and death rate when CAS was performed in the first 2 weeks of onset of neurologic symptoms compared with other symptomatic patients.[30] A few small single center series have published results that indicate it is safe to perform CAS acutely; Setacci et al.[26] presented results from 26 patients with TIA that were treated with CAS within 48 hours with a stroke/death rate of 3.8%. Wach et al.[25] published results from their institution in 2013; 221 patients were analyzed in total. Patients treated urgently (0–2 days) or early (3–7 days) did not have inferior results compared with those treated later. These results are thus consistent with the present study, and are summarized in Table 4.

In a pooled analysis from patients randomized in the ICSS, EVA-3S and SPACE studies, Rantner et al.[28] found that patients treated with CAS within 7 days had a stroke or death rate of 9.4%, compared with 8.1% if treated after 8–14 days and 7.3% when treated after more than 2 weeks from the qualifying event.

For CEA there are data on the risks of early compared with later interventions. A recent meta-analyses and a large cohort study could not find a higher peri-operative stroke and death rate if the patients underwent CEA in the subacute phase.[32,33] Several small series have published CEA results in the acute phase that are the same as delayed surgery,[16–18,34–36] and, just recently, a retrospective analysis from Rantner et al.[37] could not detect any significant differences between patients undergoing CEA in the within 2 days compared with delayed operation. On the contrary, a recently published study from Sweden demonstrated a very high incidence of peri-operative complications for patients operated on by CEA within 48 hours.[14] It has been debated, however, if a possible high complication rate could be justified when compared with the significant risk of stroke on medical treatment alone, if surgery is delayed.[38,39] The early risk of recurrent stroke with only medical treatment is also high in patients with recently symptomatic carotid stenosis.[1–9]

The strength of this study is that it is a large population based study investigating the risks of urgent CAS. It has national coverage and reflects the clinical reality in a small country. Data quality on outcomes is good with few missing values. In the study the median delay was 13 days from symptom to stenting. More than half (56%) were treated within 2 weeks of symptoms. This could be compared with the pooled results from the randomized trials by Rantner et al.,[28] where 36% were stented within 2 weeks and the median delay was 29 days. Also, in that analysis there were missing data on the delay for 15% of stented patients.

However, small numbers limit this report, especially since few patients underwent CAS within 2 days of the onset of symptoms. A type II error when looking at only those stented within 48 hours cannot be excluded. The risk of stroke and death resulting from CAS is relatively low, and very large sample sizes are often required to reduce confidence intervals. The selected material limits the generalizability of the study. The indications for the endovascular approach in Table 1 show that many of these patients would have been suboptimal for open surgery and might have an increased overall risk.

Table 4. Studies analyzing stroke or death after CAS in relation to timing.

	Time to CAS (days)			
	0–2	3–7	8–14	15–180
Wach et al. 2013[25]	7.1% (5/70)	4.5% (4/88)	2.8% (1/36)	0% (0/27)
Rantner et al. 2013[28]		9.4%[a] (13/138)	8.1% (19/234)	7.3% (78/1062)
Topakian et al. 2007[29]			26%[b] (6/23)	1.9% (1/54)
Gröschel et al. 2008[27]			7.0%[c] (10/142)	10.0%[d] (17/178)
Setacci et al.[26,e]	3.8% (1/26)			

[a] 0–7 days.
[b] 0–14 days.
[c] 0–13 days.
[d] 14–180 days.
[e] Only patients with transient ischemic attack included.

CONCLUSION

In this national registry study, CAS performed within 1 week of the onset of a neurological event was not associated with additional risk of suffering a peri-operative complication compared with those treated subsequently.

CONFLICT OF INTEREST

None.

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